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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/827,133	04/19/2004	Michael S. Allen	6704-29	2875

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EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/827,133	ALLEN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,9-11,15,16,18-23,25,26,30 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3,9,15,16,18-23,25,26 and 30* is/are allowed.

6)☒ Claim(s) *2, 4, 6, 10, 11 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/10/2006 has been entered.

Receipt is acknowledged of an amendment, filed 5/10/2006, in which claims 1, 2, 4, 9-11, 15 and 18 were amended, and claims 30-31 were newly added. Currently, claims 1-4, 6, 9-11, 15-16, 18-23, 25-26 and 30-31 are pending and under consideration.

Response to Arguments - Claim Objections

The objection of claims 24 and 27 is moot in view of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 6, 10, 11 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 2 recites the limitation "the amino acid sequence" in line 3. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "an amino acid sequence."

Claim 6 is vague and indefinite in that the metes and bounds of the term "derived from bacteria" are unclear. The term "derived from a bacteria" is unclear in that one of ordinary skill in the art would not know how much one could vary the nucleic acid sequence isolated from the species of bacteria recited in the claim in terms of the primary nucleic acid sequence and function of the protein, for example, and meet the limitations of the claimed invention.

Claim 10 recites the limitation "the amino acid sequence" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "an amino acid sequence."

Claim 10 recites the limitation "the tail-specific protease" in lines 3-4. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "a tail-specific protease."

Claim 11 is vague and indefinite in that the metes and bounds of the term "derived from bacteria" are unclear. The term "derived from a bacteria" is unclear in that one of ordinary skill in the art would not know how much one could vary the nucleic acid sequence isolated from the species of bacteria recited in the claim in terms of the primary nucleic acid sequence and function of the protein, for example, and meet the limitations of the claimed invention.

Claim 11 recites the limitation "LuxB" in line 2. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to depend from claim 10, which would provide proper antecedent basis for the term "LuxB."

Claim 31 is vague and indefinite in that the metes and bounds of the term "derived from bacteria" are unclear. The term "derived from a bacteria" is unclear in that one of ordinary skill in the art would not know how much one could vary the nucleic acid sequence isolated from the species of bacteria recited in the claim in terms of the primary nucleic acid sequence and function of the protein, for example, and meet the limitations of the claimed invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.** This rejection was made in the Office action mailed 2/10/2006 and has been rewritten to address the amendment to claim 4 in the reply filed 5/10/2006.

Claim 4 is drawn to a nucleic acid construct comprising at least one modified protein selected from the group consisting of: a modified LuxA and a modified LuxB, further comprising LuxC, LuxD, and LuxE.

The specification teaches that the LucCDABE operon contains five genes necessary for self-sustained bioluminescence in bacteria: LuxAB is a luciferase, which catalyzes the light-producing reaction; LuxCE is a multi-component enzyme that converts myristic acid to a fatty aldehyde substrate for the light-producing reaction; and LuxD is a transferase that assists LuxCE

(e.g. paragraph bridging pages 5-6). The specification teaches nucleic acid constructs comprising *luxA* and *luxB* genes in addition to *luxC*, *luxD*, and *luxE* genes (e.g. page 16, lines 22-27). Claim 4 reads on embodiments where the nucleic acid construct comprises *luxA*, *luxC*, *luxD*, and *luxE* genes, or a construct comprising *luxB*, *luxC*, *luxD*, and *luxE* genes. These combinations are not supported by the specification, claims or drawings as originally filed. The response does not point to portions of the specification, claims or drawings as originally filed as support for the amendment of claim 4.

Therefore, claim 4 represents a departure from the specification, claims and drawings as originally filed.

Claims 2 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This ground of rejection has been changed to address the amendments to the claims in the reply filed 5/10/2006.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims encompass a nucleic acid construct encoding a modified LuxB protein comprising an amino acid sequence in its carboxy terminal sequence that

specifically binds to a tail-specific protease. The carboxy terminal sequence must be capable of conferring a decreased half-life to the LuxB protein in an *E. coli* cell relative to a wild-type LuxB protein in an *E. coli* cell.

Breadth of the claims: The claims are narrow in that the LuxB protein encoded by the nucleic acid must be modified by a tail-specific protease sequence.

Guidance of the specification and existence of working examples: The specification teaches that the products of the LuxAB genes encode a heterodimeric bioluminescent catalyzing enzyme and have been isolated from several bioluminescent bacteria including *Photorhabdus luminescens, Vibrio fisheri* and *Vibrio harveyi* (e.g. page 2, lines 3-10). The specification envisions modifications of LuxA and LuxB to allow rapid degradation via cellular proteolytic pathways, such as by tail-specific proteases in bacterial cells and by a ubiquitin-proteosome pathway in eukaryotic cells (e.g. page 3, lines 1-23; paragraph bridging pages 9-10).

The specification teaches the construction of the following plasmids: (1) pAaavB, which contains the luxA gene modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYAAV (SEQ ID NO: 8), and the wild type luxB, (2) pAlaaB, which contains the luxA gene modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYALAA (SEQ ID NO: 9), and the wild type luxB, (3) pAasvB, which contains the luxA gene modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYAASV (SEQ ID NO: 10), and the wild type LuxB, (4) pABaav, which contains the luxB gene modified to include the gene sequence of the 11-amino acid carboxy-terminal tag AANDENYAAAV (SEQ ID NO: 8), and the wild type LuxA, (5) pAaavBaav, which contains the luxA and luxB genes modified to include the gene sequence of the 11-amino

acid carboxy-terminal tag AANDENYAAAV (SEQ ID NO: 8) (e.g. pages 13-14). To determine the effect of the carboxy-terminal peptides on the half-life of the LuxAB luciferase protein, the plasmids were transformed into *E. coli*. The plasmid pABaav did not result in a decrease in half-life (e.g. page 15, lines 16-19). The specification teaches that modifications of the luxA gene with the carboxy-terminal peptides decreased the half-life, whereas modifications of luxB had no effect (e.g. pages 15-16).

The specification teaches the construction of luxAcln and luxBcln, which contain the PEST-rich 178 amino acid carboxy-terminus of the G1 cyclin Cln2 (e.g. page 16, lines 15-21). The specification teaches that the luxAcln construct did not show a significant rate of decline in bioluminescence in yeast cells, whereas the luxBcln construct had a decreased half-life in yeast cells.

Thus, the specification teaches that luxA protein comprising a peptide selected from the group consisting of SEQ ID NOS: 8, 9 and 10 has a decreased half-life in *E. coli*, and a luxB protein comprising the PEST-rich 178 amino acids of G1 cyclin Cln2 has a decreased half-life in yeast cells, relative to the wild-type proteins in the same cell type.

Predictability and state of the art: As evidenced by the examples taught in the instant specification, the nature of the invention is unpredictable. For example, the addition of the peptide of SEQ ID NO: 8 to luxA results in a decreased half-life of the protein relative to wild-type luxA, whereas the same modification to luxB has no effect. Modification of LuxB to include the PEST-rich 178 amino acid carboxy-terminus of G1 cyclin Cln2 results in a decreased half-life relative to wild-type luxB, whereas the same modification to luxA has no effect. Thus, the modification of luxA and/or luxB to decrease the half-life is unpredictable.

In the response filed 11/9/2005, Applicant acknowledges that the nature of the invention is "notoriously unpredictable" (e.g. page 12). As evidence of the unpredictable nature of the invention, the response points to the working of the examples of the specification, which are discussed above and on page 12 of the response. Further, the response states, "Adding an exogenous peptide sequence to LuxA or LuxB could have any number of consequences that could result in failure of the component to function." See the second paragraph on page 12 of the response.

The half-life of a protein in one cell type does not predict the half-life of a protein in another cell type. Andersen et al (Applied and Environmental Microbiology, Vol. 64, No. 6, pages 2240-2246, of record) teach the addition of a nucleic acid encoding a peptide of instant SEQ ID NO: 8, 9 or 10 to green fluorescent protein (Gfp) (e.g. page 2240, paragraph bridging columns; page 2243, Construction of unstable Gfp variants; page 2241, Plasmids; Table 1). Andersen et al state, "the half-life estimates obtained in the experiments presented are not to be taken as absolute, fixed values. The protease reaction resulting in degradation of Gfp may be dependent on strains, growth conditions, specific features of the surroundings, competing targets in the cell, etc." (see the paragraph bridging pages 2244-2245). Thus, the effect of a protein modification in one cell type or in an *in vitro* assay does not predict the effect in another cell type.

Amount of experimentation necessary: The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to make and use a modified LuxB, wherein the half-life of the modified protein when expressed in a cell is shorter than the half-life of the wild-type protein in

an *E. coli* cell. Because the specification teaches that the addition of a tail-specific protease sequence does not alter the half-life of the LuxB protein in an *E. coli* cell, the quantity of experimentation would be large.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 2 and 10 are not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 112

With respect to the rejection of claim 4 (new matter), Applicant's arguments filed 5/10/2006 have been fully considered but they are not persuasive. The response asserts that claim 4 no longer includes the limitation of a purified nucleic acid that encodes all proteins necessary for production of bioluminescence without addition of an exogenous substrate. However, the claim still requires the combination of LuxA, LuxC, LuxD and LuxE, or the combination of LuxB, LuxC, LuxD and LuxE, which are not supported by the instant specification as originally filed.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Applicant's arguments, see pages 8-12, filed 5/10/2006, with respect to the rejection of claims 1, 3-4, 6-9, 11, 15-23 and 25-26 under 35 U.S.C. 112, first paragraph (scope of

enablement) have been fully considered and are persuasive. The previous rejection of claims 1, 3-4, 6-9, 11, 15-23 and 25-26 has been withdrawn.

With respect to the rejection of claims 2 and 10 under 35 U.S.C. 112, first paragraph (enablement), Applicant's arguments filed 5/10/2006 have been fully considered but they are not persuasive.

Claims 2 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not teach how to make and use a nucleic acid encoding a modified LuxB protein comprising a carboxy terminal sequence that specifically binds to a tail-specific protease, resulting in a decreased half-life in an E. coli cell relative to a wild-type LuxB protein in an E. coli cell. The working examples of the specification clearly demonstrate that the addition of a tail-specific protease sequence to the C-terminus of the LuxB protein does not alter the half-life of the protein in an *E. coli* cell (e.g. pages 15-16).

The response does not provide evidence that the claimed modification of the encoded LuxB protein results in the claimed reduction in half-life. Accordingly, the remarks provided on pages 8-12 of the reply are not persuasive.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

Claims 1, 3, 9, 15-16, 18-23, 25-26 and 30 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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jad

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PRIMARY EXAMINER